REMARKS

I. Preliminary Remarks Regarding Amendments

The Applicants do not intend by any amendments to abandon the subject matter of any claim that has been presented, and reserve the right to pursue subject matter of claims as originally filed during prosecution of this application or in subsequent applications, such as continuing applications. Claims 1-8, 10, 11, 46-48, and 59-64 are pending and currently being examined. A marked-up version of the amended specification is set forth in **EXHIBIT A**; a marked up version of the amended claims is set forth in **EXHIBIT B**; and the claims as they appear after entry of the foregoing amendment are set forth in **EXHIBIT C**.

An information disclosure statement (IDS) was filed on March 18, 2002. If additional fees are required for consideration of the IDS, the Patent Office may charge such fees to deposit account no.: 13-2855.

The Applicants have noted the Examiner's objection to the specification regarding the amino acid position numbering in Example 9 (pages 96-97) and have amended the specification accordingly. It would be apparent to the reader after examination of the sequence of the single nucleotide polymorphism (SEQ ID NO:18) that there were some typographical errors in the written comparisons of the sequences, and it also would be apparent what the corrections would be. In addition, the Applicants have amended the specification to remove other typographical errors.

The foregoing amendments to the specification and claims include no new matter.

II. Patentability Remarks

A. The Rejections Under 35 U.S.C. 112, First Paragraph, for Lack of Written Description Should Be Withdrawn

The Examiner rejected claims 1-8, 10, 11, 46-48, and 59-64 under 35 U.S.C. § 112, first paragraph, for allegedly lacking adequate written description. The Examiner has alleged the following reasons for rejection: 1) the hybridization

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conditions in claim 1 are not specifically rendered and therefore the claimed genus is not sufficiently described; 2) claim 2 does not have sufficient support for the claimed genus; 3) claims 3 and 59 lack limitations in structure and function to identify members of the genus; and 4) claims 4-8, 10, 11, 46-48, and 59-64 depend on the DNAs of claims 1-3 and are therefore included in the rejection as comprising product lacking sufficient written description. The Applicants respectfully traverse this rejection and submit that the claims, as originally filed, are adequately described in the specification.

Moreover, the basis alleged for this rejection is now moot in consideration of the amendments to the claims. To expedite prosecution, the Applicants have amended claims 1-3 and 59 to remove references to "hybridization" and other language which was deemed objectionable. The claimed polynucleotides are all defined with combination of structural and/or functional limitations which render the basis for rejection moot.

The Applicants have amended claims 2 and 59 to nucleotide sequences encoding allelic variants or splice variants to their claimed nucleic acid sequences to include those demonstrating "human E3α ligase activity," thus providing a structure:function attribution to identify members of the claimed genus. An allelic variant of SEQ ID NO: 1 (SEQ ID NO: 18) with a single nucleotide polymorphism (SNP) that encodes a polypeptide variant of SEQ ID NO: 2 (SEQ ID NO: 19) was already described in the specification (see Example 9, page 97, line 23 through page 98, line 12). Furthermore, the Applicants have defined the term "allelic variant" in the specification (at p. 13, lines 18-20) as referring to one of several possible naturally occurring alternate forms of a gene occupying a given locus on a chromosome of an organism or a population of organisms. Thus, the specification provides written descriptive support for two alleles of human E3α ligase within the scope of the claimed genus: two polynucleotides (SEQ ID NOS: 1 and 2) which encode two polypeptides (SEQ ID NOS: 18 and 19, respectively). It is understood that these and other allelic variants possess substantial sequence which defines the genus. Taken together, one of skill in the art would recognize that the Applicants were in possession of the claimed genus.

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The claimed invention meets the requirements of "Allelic Variants" set forth in Example 11 of the "Written Description Guidelines" published by the United States Patent and Trademark Office. As noted above, it is universally recognized that allelic variants possess substantially similar structure (sequence). The Applicants have disclosed two species of the claimed genus and members of the claimed genus can be identified by common attributes, which are described in the amended claims as those demonstrating "human E3α ligase activity," thus providing a structure:function attribution.

Consequently, the rejections under 35 U.S.C. § 112, first paragraph, are rendered moot by the amendments, and the rejections should be withdrawn for these claims and all claims which depend from them.

B. The Rejections Under 35 U.S.C. § 112, First Paragraph, for Lack of Enablement Should Be Withdrawn

Claims 1-8, 10, 11, 46-48, and 59-64 have also been rejected under 35 USC § 112, first paragraph, for allegedly not providing enablement for the broad scope of claims, which were alleged to encompass all modifications and fragments of any sequence that comprises a fragment of SEQ ID NO: 2 with unspecified functions or variants of unspecified structure. The Applicants respectfully traverse this rejection and submit that the claims, as originally filed, are fully enabled by specification.

Moreover, this rejection is now moot in consideration of the amendments to the claims. The Applicants have amended claims 1-3 and 59 by defining the claimed sequences with a combination of structural and/or functional limitations that are enabled by the specification. For example, the variants of claim 2 all possess a recited sequence relationship to SEQ ID NO: 2 and retain human E3α ligase activity. The application teaches one how to make and use such variants without undue experimentation.

In view of the foregoing comments and the amendments to the claims herein, claims 1-8, 10, 11, 46-48, and 59-64 are fully enabled by the present specification and

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the rejection of the claims under 35 U.S.C. § 112, first paragraph, should be withdrawn.

C. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

Claims 1-8, 10, 11, 46-48, and 59-64 were rejected under 35 USC § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that the Applicants regard as their invention. Specifically, the claims were rejected allegedly for: 1) not defining the specific function of "activity;" 2) not defining exact hybridization conditions; 3) confusing language in claims 2(b) and 61-64; 4) an error in the referral of claim 60; and 5) for confusing language in claims 61-64 as using "a diagnostic reagent." The Applicants respectfully traverse this rejection, because the claims as filed were clear to the reader.

Moreover, this rejection for indefiniteness is now moot in consideration of the amendments to the claims. The Applicants have amended claims 1-3 and 59 to recite a specific "E3α ligase activity" and eliminated claim language relating to "hybridization." The Applicants have amended claim 2(b) to remove the alleged confusing language. The Applicants have amended claim 60 to properly refer to claim 59. The Applicants have adopted the Examiner's suggestion to amend claims 59-62 to recite "reagent" instead of "diagnostic reagent," and have thus obviated the rejection to these claims and the claims that depend from them.

For these reasons, the rejection under 35 U.S.C. § 112, second paragraph, should be withdrawn.

D. The Rejections Under 35 U.S.C. § 102(b) Should Be Withdrawn

The Patent Office has also rejected all pending claims under 35 USC § 102(b) as allegedly being anticipated by the following references: 1) Hillier *et al.* for teaching an EST of 682 bp that is 99.3% identical to SEQ ID NO: 1 and therefore will

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hybridize thereto under moderate or highly stringent conditions; 2) Strausberg *et al.* for teaching an EST of 641 bp that is 99.5% identical to SEQ ID NO: 1 and will hybridize thereto under moderate or highly stringent conditions; and 3) Varshavsky *et al.* (hereinafter Varshavsky) for teaching a murine UBR1 that is 86% identical to SEQ ID NO: 1 and will hybridize thereto under moderate or highly stringent conditions.

To invalidate a claim for "anticipation" under 35 U.S.C. § 102, a single reference must identify each and every feature recited in the claim sought to be invalidated. Scripps Clinic and Research Foundation v. Genentech, Inc., 927 F.2d 1565, 1576 (Fed. Cir. 1991). The Applicants have amended the claims to exclude the subject matter described by Hillier *et al.*, Strausberg *et al.*, and Varshavsky. For example, the ESTs of Hillier *et al.* and Strausberg *et al.* fail to encode a protein having the activity recited in, e.g., claims 2, 3, and 59. The murine UBR1 of Varshavsky fails to satisfy the 95% identity limitation of claim 2. For these and other reasons, the rejection of claims 1-8, 10, 11, 46-48, and 59-64 under 35 U.S.C. § 102(b) should be withdrawn.

E. The Rejections Under 35 U.S.C. §§ 101 and 112, First Paragraph, Should Be Withdrawn

The Patent Office has also rejected claims 59-64 under 35 U.S.C. § 101 for an alleged lack of specific and substantial or well established utility, and alleges that neither the specification nor the art of record disclose any disease or conditions that can be diagnosed with SEQ ID NO: 1. These claims have also been rejected under 35 USC § 112, first paragraph, because the Examiner has alleged that one skilled in the art would not know how to use the claimed invention. The Applicants respectfully traverse the rejection.

The specification provides clear assertions of utility for human E3α ubiquitin ligase. The specification presents a thorough discussion of how E3 ubiquitin ligases function in normal physiological and pathological processes (see p. 2, line 8 through p. 4, line 14). E3α ubiquitin ligase binds directly to N-terminal amino acids on proteins targeted for degradation and catalyzes the transfer of ubiquitin from the E2

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carrier enzyme to the target protein. The specification also provides examples which demonstrate that: 1) huE3α accelerated the ubiquitination of cellular proteins and ubiquitin conjugation to α-lactobumin, a bona fide N-end rule substrate (see Example 10, pp. 97-99); and 2) there was elevated huE3α expression in cachexia (see Examples 11 and 12, pp. 99-104). E3 ubiquitin ligases mediate the ubiquitination of diverse regulatory and signalling proteins and are involved in many normal physiological processes, such as protein degradation essential for the control of gene transcription, cell signaling, and cell cycle regulation. Even the Patent and Trademark Office recognizes that sequences in this family are useful, as witnessed by the issuance of the Varshavsky patent (cited by the Examiner in the Office Action at p. 12).

Furthermore, the specification provides many examples of how the huE3α nucleic acid molecules, polypeptides, and antagonists thereof can be used to treat, diagnose, and/or prevent a number of diseases, conditions, and disorders "not limited to cachexia" (see p. 63, lines 13-20). In fact, E3 ubiquitin ligases have been found to be crucial components of serine/threonine kinase receptor turnover (Kavsak *et al.*, *Molecular Cell* 6:1365-1375, 2000), nerve cell function (Araki *et al.*, *J Biol Chem* 276:34131-34141, 2001), and the transition from the G_1 phase to the S phase in cell cycle regulation (Koepp *et al.*, *Science* 294:173-177, 2001). Moreover, it has been shown that mutations in E3 ubiquitin ligases can contribute to disease pathogenesis. For example, mutations in the parkin gene, an E3 ubiquitin ligase, cause autosomal recessive inherited juvenile parkinsonism (ARJP) (Fishman and Oyler, *Curr Neurol Neurosci Rep* 2:296-302, 2002). Aberrant regulation of these normal physiological processes can lead to many pathological conditions.

Finally, although cachexia may be diagnosed visually as the Examiner asserts, there is published scientific evidence to suggest that the upregulation of ubiquitin in human gastric cancer is **an early feature that precedes any clinical sign of cachexia** (Bossola *et al.*, *Am J Physiol Regul Integr Comp Physiol* 280(5):R1518-1523, 2001; attached hereto as **Exhibit D**). Therefore, the Applicants maintain their position that

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a diagnostic reagent for this condition early in the course of cancer demonstrates a specific, substantial, and credible utility.

Thus, the Applicants contend that the experimental evidence detailed above and in the specification demonstrates that there are many uses for a diagnostic reagent comprising a DNA encoding SEQ ID NO: 2 as is claimed herein. Accordingly, in view of the foregoing comments and the amendments to the claims herein, the Applicants submit that claims 59-64 demonstrate a credible, specific, and substantial utility and therefore, respectfully request that the rejection of the claims under 35 U.S.C. §§ 101 and 112, first paragraph, be withdrawn.

III. Conclusion

In view of the foregoing comments and amendments, the Applicants submit that the claims are in a condition for allowance and early notification thereof is respectfully requested. Should the Examiner wish to discuss any aspect of the present application, she is urged to contact the undersigned at the telephone number indicated.

Respectfully submitted,

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